

REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-5, 7, 22, and 23 are under examination in this application. Claim 1 has been amended.

No new matter has been added by this amendment. Support is found throughout the specification and from the pending claims.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

II. THE REJECTIONS UNDER 35 U.S.C. § 103(A) ARE OVERCOME

Claims 1-5, 7, 22, and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Baker, *et al.* (U.S. Patent No. 6,558,422 B1) in view of Vacanti, *et al.* (U.S. Patent No. 5,759,830) and Gilbert, *et al.* (Transplantation, 56(2):423-427, August 1993). Applicants respectfully traverse the rejection.

For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). There must also be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference or to combine reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). It is respectfully submitted that the cited references, taken either alone or in combination, fail to provide a reasonable expectation of success in practicing the claimed invention. Additionally, given that the Gilbert and Vacanti references teach effects opposite to that of Baker (i.e., angiogenesis versus anti-angiogenesis), there can be no motivation to combine or modify the reference teachings.

A. **Baker is not entitled to the priority date of March 26, 1999.**

Baker describes biomedical structures having indentations selectively coated with a substance possessing a desired biological quality. TSP-2 is said to be one such substance. In citing Baker as a reference against the present application, the Examiner apparently relies on the teaching in Baker where it is stated that "...rats were treated with implantable devices, disks containing thrombospondin-2 (TSP-2)...".

Review of the corresponding provisional application, U.S. Application Serial No. 60/126,545 ("the '545 application"), filed on March 26, 1999, however, reveals that Baker neither disclosed the use of TSP-2, nor presented any data relating to TSP-2. In fact, the '545 application is silent with respect to TSP-2 (a copy of the '545 application is provided for the Examiner's review). The '545 application discloses only the schematic diagram entitled "Process Overview", wherein step 6 reads "After the *in-vitro* studies are completed the material could be implanted in rats to test its ability to induce angiogenesis *in vivo*." The need for *future* experimentation constitutes the full extent of guidance provided to the person of ordinary skill in

the art. This disclosure cannot be deemed to provide the requisite enablement and/or written description necessary to support a claim of priority for the treatment of rats with disks containing TSP-2, or the use of TSP-2 in general.

Accordingly, Baker is not entitled to the March 26, 1999 priority date for the above-referenced teachings cited by the Examiner. Thus, the effective priority date becomes March 22, 2000, which does not precede the date of priority of the present application, that is, March 31, 1999. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

B. The person of ordinary skill in the art would not find motivation to modify or combine the teachings of Baker.

Even if Baker would qualify by date as prior art against the present application—and it should not—Applicants further submit that the skilled person would have been entirely lacking in motivation to modify or combine the teachings of Baker.

The present invention is directed to methods and reagents for producing clinically effective amounts of therapeutic biologics such as the anti-angiogenic protein thrombospondin-2 (TSP-2) *in vivo*, as well as to methods and reagents for treating disorders characterized by abnormal tissue proliferation such as cancer using anti-angiogenic inhibitors expressed by biologically engineered cells of biodegradable polymeric matrices. In one embodiment, the invention constitutes a method for treating a disorder characterized by excessive proliferation of tissue comprising implanting a cell-matrix structure having attached thereto cells that stably express TSP-2 or a fragment thereof.

Baker describes biomedical structures having indentations selectively coated with a substance which can be TSP-2. Baker does not, however, teach or suggest that the "biologically active substance" is a cell, let alone a cell stably expressing TSP-2. In effect, Baker does not contemplate cell-based therapy and therefore, provides no reasonable expectation of success in practicing the claimed invention. This deficiency becomes increasingly pronounced if only the '545 application is considered, as the '545 application fails to provide any teaching whatsoever for TSP-2.

The Examiner relies on the combination of Baker with Vacanti and Gilbert to compensate for the deficiencies of Baker. Yet the skilled person would not have been motivated to combine

the teachings of Baker with those of Vacanti and Gilbert or modify Baker in view of Vacanti and Gilbert, as Gilbert and Vacanti teach effects directly opposite to that of Baker.

Vacanti describes cell-scaffold compositions for growing cells to produce functional vascularized organ tissue *in vivo*. Of note, success in producing the functional organ equivalent is said to depend "on the ability of the implanted cells to attach to the surrounding environment and to stimulate angiogenesis." (column 5, lines 42-44, emphasis added).

Gilbert describes the use of biodegradable polymer fibers in the transplantation of genetically modified cells to deliver a therapeutically useful product. Of note, the genetically modified cells are observed, after implantation, to be participating in the formation of fibrous networks (page 425, first column, last paragraph and figure 3). Furthermore, it is stated that "The polymer surface allows for attachment of angiogenic factors..." (page 426, second column, first paragraph, emphasis added).

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95 (Fed. Cir. 1983). The person of ordinary skill in the art would not have been motivated to combine or modify the teachings of Baker with those of either Vacanti or Gilbert (let alone both). In fact, Vacanti's and Gilbert's findings of increased angiogenesis and fibrous network growth would have precluded the person of ordinary skill in the art from relying upon their teachings in developing a delivery system of some sort for TSP-2 based on Baker, since the latter instead advocates reduced angiogenesis and fibrous capsule growth. The person of ordinary skill in the art would have no reason to combine or modify references teaching directly opposite effects, as is the case with the cited references.

Moreover, Applicants further submit that the skilled person would have literally been taught away from the present invention, which teaches anti-angiogenic therapy, by Vacanti and Gilbert, which instead teach angiogenic therapy. The very same observation of opposite effects that keeps the person of ordinary skill in the art from combining the teachings of Baker with those of Vacanti and/or Gilbert likewise teaches away from the present invention.

The person of ordinary skill in the art having motivation neither to combine Baker with Vacanti and Gilbert, nor to consider the latter references at all in view of the teachings of angiogenesis therein, would not find the invention as disclosed in claim 1 to be obvious in view of the cited references. If an independent claim is non-obvious under 35 U.S.C. 103, then any claim depending therefrom is non-obvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Claims 2-5, 7, 22, and 23 depend from claim 1. Having established the non-obviousness of claim 1, claims 2-5, 7, 22, and 23 are, by extension, also non-obvious.


Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the amendments and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application, reconsideration, and withdrawal of the objections to and rejections of the application, and prompt issuance of a Notice of Allowance are respectfully requested. No fee is believed to be due for entry and consideration of this paper, however, any fee occasioned by this paper may be charged, or overpayment credited to, Deposit Account No. 04-1105.

Respectfully submitted,

May 23, 2005


Amy Leahy, Registration No. 47, 739
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
(203) 353-6839
Attorneys for Applicant

Customer No. 21874